DRUG INFORMATION ASSOCIATION

FDA/DIA SCIENTIFIC WORKSHOP ON FOLLOW-ON PROTEIN PHARMACEUTICALS

BREAKOUT SESSION D

CLINICAL PHARMACOLOGY STUDIES

Monday, February 14, 2005

3:30 p.m.

Marriott Crystal Gateway
1700 Jefferson Davis Highway
Arlington, Virginia

PARTICIPANTS

MODERATORS:

DENA HIXON, M.D.

HAE-YOUNG AHN, PH.D.

HONG ZHAO, PH.D.

DAVID PARKINSON, M.D.

WILLIAM SCHWIETERMAN, M.D.

P R O C E E D I N G S

DR. HIXON: It's just about 3:30, so if everybody could take a seat and get ready, we'll have the last breakout session for the day

Hello everybody, and thanks for having in there for the last session of the day.

I'm Dena Hixon. I'm the Associate Director for Medical Affairs in the Office of Generic Drugs. And I've been asked to take the role of lead FDA moderator for this breakout session on Clinical Pharmacology-Pharmacodynamics and Pharmacokinetics in the evaluation of follow-on protein products, or follow-on biologics if you like that term better.

Unlike the open public hearing that was held in September, this particular meeting is intended to solicit open scientific discussion from the audience. We have an official transcriptionist present to accurately record proceedings of this meeting. Any person wishing to comment at this meeting is asked to please use the microphone in the center aisle, and clearly state your name and

your affiliation.

And since some people will be talking more than once, and others may not remember who everyone is, please state your name each time that you want to speak.

We'd like you to also provide either a business card or clearly print your name and affiliation on one of the notepads on the table to provide to the transcriptionist.

We remind you that this is intended to be an exchange of scientific information and ideas regarding the information needed to evaluate a protein product that purports to be the same as a product already on the market and no longer protected from competition by valid patent or exclusivity. This is not intended to be a debate about whether there can be or should be an abbreviated mechanism for bringing such a product to the market.

[Slide.]

We have three questions that are actually in our program for today that this session is

supposed to address. These questions are: number one, what information does a PK study provide? Number two: what additional information of value would a PD study provide? And, number three: what factors affect study design and establishment of acceptable limits for pharmacokinetic and pharmacodynamic comparison?

In order to allow everybody to get a chance to speak, we're asking that you keep your remarks to a maximum of three to five minutes. If you're not finished by that time and others are wanting to speak, the chair reserves the prerogative to ask you to relinquish the microphone to the next speaker.

Any scientific data discussed at this forum that has not been previously submitted to the docket is to be submitted to that docket by the individual discussing the data. The Docket Number is 2004N-0355.

We also remind the audience that FDA has no established policy with regard to the issues at hand. No discussion of any FDA person should be

interpreted as agency opinion or policy, but rather the observations or opinion of the individual.

This is a repeat of the same session that we just had, which ended half an hour ago. And we have two additional FDA moderators, and two industry moderators.

Dr. Hae-Young Ahn did a presentation at the last plenary session. She has been a team leader in the Office of Clinical Pharmacology and Biopharmaceutics in CDER since 1995, working mostly with the Division of Metabolic and Endocrine Drug Products. She's also been a member of several coordinating committees and working groups, such as the Complex Drug Substance Coordinating Committee, Biopharmaceutical Coordinating Committee, and Non-glycosylated Peptide Working Group. And she has received many CDER awards.

During this session Dr. Ahn will be recording highlights of the discussion which will be projected on the screen in place of a flip chart for the convenience of the audience. She will also assist in asking for clarification from speakers as

needed, to assure accuracy of breakout session summary.

Dr. Hong Zhao is a senior reviewer of Clin-Pharmacology and Biopharmaceuticals in CDER. She has reviewed numerous neuropharmacology drug products, and has received many FDA awards for her outstanding review work. She also has presented Clinical Pharmacology Considerations: A Case Study to FDA Workshop on Proteins and Peptides, Scientific Foundation for Review in 2004. She also recently lectured on pharmacokinetics of large molecules and biotech-derived products for an FDA course on pharmacokinetic and toxicokinetic concepts, and application in drug development and regulation.

During this session, Dr. Zhao will be taking notes and asking for clarification, and posing additional questions as needed regarding the use of pharmacokinetic and pharmacodynamic endpoints in the evaluation of follow-on products.

In addition, we have two industry moderators who were recommended by the planning

committee members representing the innovator and generic pharmaceutical industry and the biotech industry.

Dr. Parkinson is vice president of Global Development and head of the Oncology Therapeutic Area at Amgen. He is Canadian-born, and received his M.D. degree from the University of Toronto School of Medicine, followed by residency training in internal medicine and clinical fellowship training in hematology at McGill University. Since that time, his career has placed him in leadership positions at Tufts New England Medical Center, M.D. Anderson Cancer Center of the University of Texas, the National Cancer Institute Cancer Therapy Evaluation Program and, in 1997, he joined Novartis and the NIH, prior to working for Novartis as head of Oncology Clinical Research and Development there. And he, of course, now is in his current position with Amgen.

Dr. William Schwieterman is an independent consultant to the pharmaceutical industry. He has a medical doctorate degree from the University of

Cincinnati School of Medicine, and also a residency in internal medicine. And he subsequently did fellowships at NIH in the National Cancer Institute, followed by a fairly long career at FDA in first reviewer and then leadership positions.

Drs. Parkinson and Schwieterman will assume the role of co-moderators and discussion leaders to assure that important considerations regarding the use of pharmacokinetics and pharmacodynamic information in the evaluation of follow-on products--as previously described--are adequately discussed in this forum.

They have each been asked to give brief introductory comments, with a few slides, to open this public discussion.

With that--Dr. Parkinson.

DR. PARKINSON: Thank you, Dena. Good afternoon, and welcome to the session.

Bill and I will make a few comments to really try to put a context around the questions we'd like to have discussion around this afternoon.

And if I could go to the first slide,

please.

[Pause.]

We've got our best people working on this.

[Laughter.]

Good. Thanks very much. You can go to the next one now, because that one's not that great.

[Slide.]

Just a few considerations--let me give you my perspective. I am not a card-carrying clinical pharmacologist, You'll realize that very, very quickly. But I am a clinical drug developer and we care an awful lot about the kinds of issues that we'll be discussing here this afternoon.

What I've tried to do is put some thoughts around the concepts that were discussed this morning relevant to the questions we need to answer this afternoon.

First of all, I think we've heard--in some extraordinary detail--that biotechnology products are incredibly process-dependent products, and that while there has been dramatic technological

improvement in our ability to assay these agents--to characterize them--there are significant limitations still in determination of analytical specifications and assays; and whether the specifications that we can determine are truly valid predictors of ultimate biological safety and potency, which is what we're all about.

In other words, there are limitations to physical-chemical testing to establish sameness. And the issue, I think, for discussion today is: okay, to what level do we have to take those physical-chemical characterizations, and what does that actually mean, in terms of tradeoffs?

Without anticipating this afternoon's discussion, it was my own view from looking at this morning's discussion that the feasibility of PK seems to be quite evident for most agents, given the new technologies, but so does the necessity of PK studies as part of any process to characterize the new biologic--the need to confirm dose, for example, in order not to put patients at risk; to avoid being surprised, despite our best attempts at

physical-chemical characterization.

Next slide, please.

[Slide.]

And then together with this need for PK, the questions that we'll be discussing here this afternoon relate to the necessity and the value of parallel PD studies--whatever they might be, particularly in settings where validated surrogates may exist.

In the absence of validated surrogates, PD studies, of course, are very difficult to perform, and raises the issue for consequent need to clinical data. And, frankly, despite all of that, the reality that a limited clinical experience does leave a certain amount of uncertainty, and so I would hope that some of the discussion this afternoon will be around what level of uncertainty, and what kinds of uncertainties, are we willing to accept as part of this process--which we all believe is necessary to have some sort of process to move towards a follow-on biologic.

So the reality is--as I've indicated--that

a limited clinical experience still leaves uncertainty, and probably will never fully establish identity, but that's probably true for lots of other things we have to deal with in our daily lives.

So, with that, I'll turn it over to Bill.

Thank you.

DR. SCHWIETERMAN: Thank you very much, David. Thank you very much, Dena.

In the interest of getting right to the discussion, I'll keep my comments brief, as requested.

A few thoughts of my own before listing some of the thoughts made in the plenary session today.

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[Slide.]

I think one of the fundamental points about this discussion about PK/PD studies is about the complexity of the issue itself with regard to a number of issues, including the complexity of the proteins, including the clinical indication,

including the analytical sensitivity of the assays being used, and so forth. So any sort of discussion about the merits of PK/PD studies--as much as we'd like to--really can't be made in isolation, but has to be made with respect to these other parameters. That would be point number one.

And the other point is that, you know, really these are about broad scientific principles, I think, that we need to derive from particular examples. So I'm very interested in the discussion that we have today with regard to what people's experiences are and so forth, with regard to these.

So, without further ado.

[Slide.]

Considerations for Discussion --and, again, these are things that were stated, I think, in the plenary session, and have merit. And I'd like to hear the audience's opinion about them.

PK studies provide information about comparability in systemic exposure --

PK studies are feasible for a majority of proteins.

PK studies may not be needed for solutions of simple protein products that are comparable analytically.

And PK studies are generally necessary if uncertainty about comparability could not be adequately minimized through characterizations of animal studies --the principle here being that PK studies again, not in isolation, are used as a measure of not necessarily just predicting clinical outcomes, but about showing differences between products. And therein lies a distinction I think needs to be borne out when we have discussion about the science.

Next slide, please.

[Slide.]

The last slide, then is: The standard 90 percent confidence interval for bioequivalence criteria are appropriate for most PK studies. Had an interesting discussion in the last breakout that this may be true or not in certain instances.

The usefulness of PD studies is, in part, a function of available outcome measures.

If PD measurements are to be included, simultaneous PK/PD studies are often preferred.

And PK/PD studies, in conjunction with adequate characterization are usually sufficient to support approvability, and in some cases interchangeability.

So, between Dave's and my lists, we have a number of different, I think, important points that are made about the utility and relevance of PK/PD studies, and looking forward to the discussion about all of these.

Thank you.

DR. PARKINSON: Thanks, Bill.

The floor is now open for comment or discussion on any of these questions. Our only goal is that nobody leaves until we answer the three questions. Otherwise, we're all in trouble--as far as I can tell.

DR. HIXON: In order for us to provide a summary to the plenary session on Wednesday morning, it may be helpful for us to discuss some of the things that we're likely to have the most

agreement on first; such as what information does a PK study provide? Do we need PK studies for these products? And what is their usefulness? And then go on to question number two, about a PD study. And with question number three, we're likely to get more lively discussion.

DR. PARKINSON: So, can we agree that we agree on the first one?

Any comments?

Katie. I knew we'd be able to get an opinion.

MS. STEIN: I guess I would raise the question that I raised in an earlier breakout session this afternoon, and that is regarding bioassays: that a bioassay measures all of these--

DR. HIXON: Excuse me, can you give us your name--

MS. STEIN: Oh, sorry--Katie Stein, Macrogenics--and I'm speaking for myself.

[Laughter.]

I'm not representing Macrogenics.

A bioassay measures all of the

heterogeneous microforms in a product. And often there isn't any information about what activity is attributed to small components of that product. And if you go to high concentrations of drug substance, as opposed to drug product, you can't always separate out those forms. So the bioassay gives you the total sum of all the microforms in the product.

And I would argue that a PK study is needed because the PK of the product will be the sum of all of the microforms in that product; and that it's very difficult to determine what the PK would be based solely on drug product, even if it's the drug product that's being administered--because of the points that Dave Parkinson made earlier, that the production of biologics is really process-related. And although you may see a certain set of biochemical forms in the drug product, not all of them can be measured, and not all those that have biological activity can be measured--unless you're really looking at a high concentrated drug substance.

And so I would argue that you do need to do PK studies to be able to pick up everything that's in that product, not all of which would be

necessarily measurable in the final drug product.

DR. PARKINSON: Is there anyone who would disagree, or want to expand on that comment?

Dr. Cosenza?

DR. COSENZA: I'm Mary Ellen Cosenza, Amgen, and I represent both myself and Amgen. [Laughs.]

I would just add to that that, you know, we know by fact that you can't extrapolate from in vitro assays to in vivo potency. So just by example, molecules where we change the glycosylation, I think it's been well published, showing that you may have less in vitro potency, and bioassays may show less activity because the molecules have been slightly changed by glycosylation. So in an in vitro sense, they bind less tightly to receptors and therefore seem less potent that way, but when put into an animal, or put into a human, they are actually more potent

because they extend the half-life.

So I just want to highlight that as an example where you cannot just tell from in vitro assay what the actual potency is, and you actually need to do an in vivo study.

DR. NOVAK: Jeanne Novak, CBR.

I think the other thing to think about what PK studies can provide, especially for therapeutic proteins where there may be a propensity for an immune response, is that you certainly can use PK studies to discern what types of differences you might have in an individual who has, in fact, moderate immune response versus one who has not. And I think that's an additional component we should think about when we plan our studies for follow-on; not just at initial presentation of a new product, but subsequent presentations.

DR. PARKINSON: Thank you.

Other questions? Comments? Are we ready to go on to the second question?

Bill?

DR. SCHWIETERMAN: The second question has to do with what additional information of value would a PD study provide?

Comments or questions?

I think the issue here really is twofold: what kind of measures might be useful for predicting clinical efficacy with PD and, secondly, about comparability itself.

You know, there are really two questions, as we've discussed before here: one is an assay that shows differences between the innovator and the follow-on, and the other one is the relevance of those assays for predicting clinical outcomes. So I'd be interested in hearing from the group about what they think about PD measurements in that paradigm, as a comparator and as a predictor.

DR. THOMAS: Adrien Thomas, Johnson and Johnson.

I guess there's no simple answer to that, because it's really highly dependent on whether you have an appropriate surrogate model for clinical outcome. And so I guess I'd just make the comment

that there's probably likely to be highly select and experience-specific.

DR. SCHWIETERMAN: Okay. Very good.

Other questions, comments, on the value of PD studies?

DR. DUCHARME: Murray Ducharme, MDS Pharma Services and University of Montreal. I guess, to my mind, the main question is: is there doubt that the two molecules can still be different after characterization and all of that?

We've seen that a slight change in a molecule can change dramatically the PK of the biologic. Therefore, in my mind, if there is doubt that the two molecules can still be different, then one absolutely needs to do a PK/PD study. Just PK is not enough, and just PD would not be enough. If you show that you have the exactly the same PK, and you have the same PD, then it will give you, really, the assurance that you're going to have the same efficacy and toxicity.

Now, of course, this assumes that you have the PD marker that is important, and the PD marker

that is used in clinical practice all the time to show that the drug is effective, for example.

DR. SCHWIETERMAN: So you're arguing--if I can paraphrase this--that it ought to be a hierarchical sort of thing, where, depending upon--and a Bayesian sort of thing, in some ways, because the more you know about the differences, the more important follow-on PK/PD studies may or may not be. Is that a reasonable summary? The PK/PD studies--I guess I don't want to put too many words in your mouth are really--their value is directly proportional to what you know or don't know going into them.

DR. DUCHARME: Yes. If you would be exactly sure that you have the same molecule, and that they're identical, then only a PK study would suffice. But if there is doubt that they can still be different, then PK is not enough.

DR. PARKINSON: Would that level of evidence be different with different categories of proteins? Is that protein-specific?

DR. DUCHARME: Umm--yes, I would think so.

I mean, if you have a very simple protein, probably you can characterize it fully. I'm going to leave this to other people that are more knowledgeable in characterization. But from a clinical pharmacology standpoint, if you feel that they are similar or identical, then PK will be enough. If there is doubt, then you need PK/PD.

DR. PARKINSON: Is this related to that topic? Do you have a new question, or--go ahead.

DR. FACKLER: I just wanted to make a comment--but I'll answer that question.

DR. PARKINSON: Great.

DR. FACKLER: Paul Fackler from Teva Pharmaceuticals.

Certainly the more complex the protein, the more uncertainty you have after the analytical characterization. I think that's just a fact of life; and that the smaller proteins, the more well-characterized proteins, leave less uncertainty. And we have examples with those having been approved through the NDA process--human growth hormone or insulin, for instance. So the

more complex the protein, the more questions you have, I think the more utility to a pharmacokinetic comparison of the two.

But the pont I wanted to make is that I think a PK study should be done when it's done, for instance, in a comparability protocol for the brand company changing the cell line, for instance, or changing the process, or changing the site--all of the things that cause the brand company to re-evaluate their product; or the change between the clinical trial batches and what's to be manufactured.

If, in the course of their comparability of the analytical comparability of the product there are questions left, and they do a PK study, well, I think, follow-on proteins naturally would require the same amount of work. I can't imagine a circumstance where you'd be doing less work under a follow-on protein comparison than you did from a clinical to a to-be-marketed batch comparison.

DR. PARKINSON: Thanks for that comment.

Dr. Seamon?

DR. SEAMON: Ken Seamon, Amgen. I want to refer back to the previous question.

We certainly agree that there's

significant value in doing pharmacokinetic studies, and pharmacodynamic studies, particularly when you are concerned about any differences in the molecule, or after a significant manufacturing change. Ultimately, we want to make sure that we're dosing patients with a safe dose of active drug.

However, I'm concerned about referencing those studies as providing support for safety. And I think that was referenced in the previous comment. Because I fail to understand, given the complexity of the safety concerns with these molecules, how one gets assurance of safety from a PK/PD study--except that type of safety that's most closely associated with the exaggerated pharmacology or activity of the protein.

So--and I'm not an expert, as Dave is, in this area--but I just fail to understand the correlation with safety.

DR. SCHWIETERMAN: Comments or questions to Dr. Seamon's response?

So there's a notion here of dissociating the efficacy with the safety issues which, you know, are very important, because safety does, in fact, come foremost.

Is there agreement that that's something that really limits the value of PK studies? I mean, it's certainly a very important question.

Dr. Thomas?

DR. THOMAS: Adrien Thomas. I think you're asking different questions, aren't you? I mean, I don't think that you're going to address a safety concern with a PK study this early, unless, as was said before, it's something like an exaggerated [noise interference] itself. That's likely to be determined through a PD study.

So I think you can't answer that question with a PK/PD study--that's correct.

DR. PARKINSON: I think where this came up before in discussion related to: could we look and discuss PK/PD studies in isolation. I forget who

brought that up. And, as a clinician, you know, we don't see PK/PD studies in isolation. This whole story ultimately is around efficacy and safety in patients. And PK/PD is an important part, but not a complete part. It may be a necessary, but it most certainly may not be a sufficient condition for establishing comparability at the safety level.

So then the issue is: well, what actually does, and are there different levels of evidence necessary for either different kinds of molecules--which was my last question. But now this question would relate to different levels of complexity related to the biology and the clinical medicine of the situation. In other words, how individualized does this thinking have to be? How important, for example, does need to consider immunogenicity in the context of a native protein, as opposed to some sort of artificially constructed protein--which, even if it's comparable, the immunogenicity issues are quite different.

Any comments on the context in which you want to use the therapeutics, as determining part

of the answers to these questions? Is that a relevant thing to bring up?

DR. SCHWIETERMAN: Interesting questions from the audience. I'll give my two cents.

I think you're absolutely right, Dave. I think almost no human study--whether it be PK, PD, clinical long-term safety--really is done in a vacuum, but rather in the context of what the potential issues might be, because one can't adequately interpret those results unless one's considered what might actually happen. So, depending upon theories you talk about--the level of immunogenicity and so forth, particular safety issues--you'd need to devise that study appropriately.

So I guess it works both ways, though. I mean, the less concerns you have about these issues, and the more you know about--and I'd be interested in hearing what the group says--about comparability between the products, then those questions don't raise to the level that they might, and you can use the PK/PD studies, as some have

suggested, in more direct ways.

So I see it--I think we see it the same in that way: it's a continuum, really.

DR. NOVAK: Jeanne Novak, CBR, again.

I think an interesting point, though, about conducting PD studies, of course, is it's obvious that there are not markers for every molecule that we're testing, and certainly what we're looking at as far as outcome measure--PK might be very valuable in comparing molecules at the initial onset, and PK assessments are very important.

But when thinking about PD, how much more it does provide in the characterization of a molecule really depends on the target. You might see intracellular enzymes, for example--if we're doing enzyme therapy targeting--where the PD marker is not going to be straightforward. In growth hormone we see markers that are longer term from the administration of the drug. In a monoclonal, where we're targeting a tumor--again, you can go down the list--those are not easy molecules to

study from a pharmacodynamic sense. Of course, establishing appropriate surrogates might be helpful, but it doesn't tell the tale, as compared to, for example, insulin, where you can certainly see the PD parameter very, very clearly, and it's very well defined.

So, that's another point that I think is important to think about. You can't always say, If we're doing PK we should be doing PD. I think you need to balance it with what you're looking for and, again, what the merits would be from that particular study.

DR. VIVEASH: Dawn Viveash, Amgen, expressing my own opinions, but I think they're rather consistent with Amgen's opinions.

I think it's important to recognize that PK studies and PD studies, I think, are very helpful for the reasons that have been articulated. And I think as others have commented on, there are also some significant limitations.

We heard from Mark Rogge an example where, when you're looking at PK you're typically looking

at blood that may not be the site of action--actually, usually is not--and therefore it doesn't really necessarily give you the insights into where the drug is actually going to have its effect. And some of the subtle changes that could impact those factors may not be detected in a simple bioequivalence study.

So I think that needs to be borne in mind. I don't think there's a one-size-fits-all solution. I think it all depends on: what's our level of understanding of the molecule, the mechanism of action, the structure-activity relationships.

I'm co-moderator for the clinical section tomorrow, so we'll get into this, I'm sure, a little bit more there. But these things are helpful, but don't necessarily obviate the need--and, actually, most of the time, in our opinion would not obviate the need--to do some clinical work.

Likewise, with the PD assessment--as has been pointed out--sometimes there are very good predictive PD assessments, and oftentimes there are

not. It's helpful, nonetheless; it is a hierarchical approach, and usually we work our way through these various steps. But, again, I think you need to look at the information in the context of what you know about that product, what's known about that indication, and how much uncertainty is there. Because if there's uncertainty, there's risk. And we can minimize the risk by collecting more data, and I think that will take us to the discussion tomorrow around needing some clinical data as well. Thank you.

DR. SCHWIETERMAN: Thank you.

Other questions, comments?

Dawn, while you're there at the microphone, let me just ask you--can I put you on the spot?--how would you categorize the uncertainty going into a PK/PD study? Would it be--I mean, what comes to my mind is related to not just the molecule, but actually to the assays that have been used to characterize that molecule. I mean, what goes through your head when you think about uncertainty--uncertainty about differences is what

we're talking about here--going into the PK/PD study?

DR. VIVEASH: Well, I think you're absolutely right, Bill--it's multiple considerations. It is based on the molecule itself; what you know around that molecule, as I've just described. I think, looking at the methodologies we have--some of the technologies are excellent, and some of them are sub-optimal. They may give us pointers in the right direction, but the assays may not be totally predictive.

And so I think, as we go through this we need to look at what information are we really deriving by each and every test we apply: do we know how that relates to the next step along the line, and to what extent can we extrapolate? Because we have to bear in mind that what we're talking about with follow-on protein products is trying to introduce products safely and effectively in a situation where there are already established therapies. We're not talking about an unmet medical need situation. You have proven products

that are safe and efficacious. So we want to set a very high standard for these.

And I don't think we should make a presumption of safety and efficacy if we can prove safety and efficacy.

DR. SCHWIETERMAN: Thank you very much.

Comments and questions? I think we're still on number two. I don't know, Dena, if you want to move to number three or not?

DR. PARKINSON: Are we ready to discuss the margins? The whole issue of certainty-uncertainty related to equivalence?

What do people think? Are the same margins that are acceptable in a small molecule setting acceptable with respect to proteins?

[No response.]

Going once, twice--sold. Okay. I guess we're in 80-125, unless anyone--

DR. HIXON: But maybe it's fair to just share with the audience what the last breakout session concluded about that.

DR. PARKINSON: We had actually--actual

physical violence--

[Laughter.]

--broke out last time. So, you missed the more exciting session. But there's still time.

DR. HIXON: Actually, our understanding--and correct me if you heard differently--

DR. PARKINSON: Mental violence--

DR. HIXON: --the last group had a fair amount of discussion about the established 80-125 limits, and the question came up: Why? Why use those limits?

And I think the bottom line was that the entire group felt that those limits are actually fairly tight limits, and if a product actually does meet those limits, that that would be very reassuring for that product.

On the other hand, nobody gave any recommendations for changing those limits to anything else, because we don't seem to have the scientific data to support other limits.

So the 80-125 that exists is basically

just because of regulatory precedent.

Any other comments?

DR. OLESON: I have a comment. Rick Oleson, Cubist Pharmaceuticals.

Going back to the PD studies, but also this question of limits--my concern is the PD assessment--PD studies--they're as good as the endpoints, the markers, you have and the reliability of those markers related to, ultimately, the safety or efficacy of the drug.

There could be a case--particularly with PD markers that are fairly variable or loose certainly in predicting human--where a PK study might show some slight differences outside the 80-125 rule, but your PD evaluation would essentially show that you're comparable or similar--or not different really; null hypothesis.

The question really is: in the context of the disease state--efficacy--is that difference in the PK divergence really going to lead to a difference in efficacy or even safety?

The other situation is, first of all: PK

and PD may be dependent upon different interactions; different receptor, different binding. And so you might have comparability from a standpoint of PK, but truly, with good markers, see a difference in PD which is really important.

So you'd have both cases. And I think it's a very complex situation. But the thing I concern myself is: basically, with the PD markers, most of them are not as tight as PK. And I do worry about the PK limits because of the types of assays we're using, whether it be ELISA or not. But PD is even worse.

And to carry those same sort of limits to PD studies is really a problem.

DR. PARKINSON: I think the suggestion was made in the last session that those limits might be appropriate for PK, but probably would not be appropriate for PD--for the exact same reasons in your scenario two. Because don't you think it's more likely that the PK would be tighter, and the PD would be all over the place?

DR. OLESON: Absolutely.

DR. PARKINSON: Given somebody who does clinical trials for a living, that's where we are.

DR. OLESON: Right. That's a problem in

interpreting, ultimately, do you have a compound that's going to have the same efficacy.

But you could get the other case where you'd have very tight analytical work for PK and see a divergence because of the patient study. But, basically, because of the PK, and the PD, and the way the drug's working, it doesn't matter. It's not clinically relevant, that PK difference.

DR. PARKINSON: On the other hand, also raised was the possibility that that PD divergences could be--as you indicated in your comments--important signal that something in that analytical similarity, something in the PK similarity is not telling you the whole story. And so two elements came up: is that an indication for a clinical trial that will try to find out whether this is of clinical relevance? The second issue that was brought up--interestingly, by an FDA reviewer who's faced this--is a setting where the

molecule could be applied in two different clinical settings. The biology may not be the same in both settings. The one setting is easy to study; validated, easy endpoints to achieve.

DR. OLESON: Tight markers.

DR. PARKINSON: Right. The other setting is complicated therapeutic setting and interpretive settings. And could one automatically assume comparability across those two settings?

DR. OLESON: They may be different. I think the point is it's complicated and you can't just make one assumption.

DR. PARKINSON: Thank you.

Please.

MR. ANDOLINA: Vincent Andolina, Teva Pharmaceuticals, U.S.A. I just wanted to point out a precedent where wider PD limits were accepted by the Office of Generic Drugs.

The guidance on Albuterol inhalation aerosol requires a PD study of various lung function tests, and I believe the confidence intervals for that are 67 to 150.

DR. THOMAS: A couple of comments. I find it interesting that you said that the previous audience found that if you had tight PK/PD limits

that that was reassuring. I assume you mean it's reassuring that you have what you think what you have applied for efficacy.

DR. PARKINSON: I think there was dissension about whether it was reassuring--the issue was--it was another piece of evidence.

DR. THOMAS: Okay. Okay. Thank you.

And the second comment I have is that often it's quite hard to set up the same assay in different sites and get it to perform. So I think the PD, by its very nature, is going to have wider limits than the PK?

DR. SCHWIETERMAN: Other comments?

DR. DUCHARME: Yes, I just want to comment on those limits.

For the PK, I think there's general agreement that 80 to 125 makes sense; that normally it should not be that variable, that it should be feasible. But from the PD standpoint, I agree with

some that have said that it may be, in some cases very variable and because of that, probably that it would make sense to maybe put forward like a scaled bioequivalence approach; something similar to what is talked about right now for small molecule drugs. Okay--so maybe something to think about.

DR. SCHWIETERMAN: Well, David, let me ask you this. I mean, is it that the PD--I mean, the PD measurements are a measure of bioactivity. I guess it's the variability around the response in in vivo systems that dictates how precise the measurements can possibly be to show equivalence.

Is that a statement you'd agree with?

DR. PARKINSON: Yes, I think so. You know, the point of this exercise is the patient. Ultimately, what we really care about is how these agents perform in patients. And I must say it has been a startling revelation to me over the last two years, as I became exposed to the whole wonderful and marvelous world of erythropoietins to find a biological system that's probably as well understood as any axis in clinical medicine, where

the readout one would have thought is as straightforward as any readout in clinical medicine; where the readout is not accepted as a validated endpoint by registration authorities; and where, frankly, the more one studies this PD marker--hemoglobin change--in literally tens of thousands of patients, the more one appreciates the remarkable complexities in the responses to those patients--some of which, no doubt are related to the drug, but which are quite challenging to parse out.

So this whole challenge that we have to reassure ourselves--and we all believe it's socially necessary. We heard this morning the drivers for the whole concept of follow-on biologics--but as a clinician I will tell you, and as a clinician involved on the innovator side, struggling with the implications even of relatively small process changes and trying to understand whether what we see in clinical trials is something important or not, it is very, very complicated. That is not a reason to say that it shouldn't be

tackled, but it is a reason to say that some of what we heard this morning, that analytical and chemical identity was enough and that it would be therefore easy to move on, I think is actually quite easy to challenge.

And what we heard here is that people are more comfortable with the concept of doing PK and PD, and realize there's a lot of variability around the PD, and there are precedents for acceptance of that. But there may be important issues in the PD variability, and the challenge will be to try to sort that out--I suspect--as a community, as we face a range of biologicals in different clinical contexts.

Any thoughts on that? But certainly that's the way I see this, is that it's not simple.

DR. SCHWIETERMAN: Let me challenge you just for a second.

There's no doubt about the variability of PD markers in patient populations. Quite frankly, clinical outcomes themselves sort of that as well; give a drug and you can have quite different

responses in different patients.

But the question on the table isn't so much the variability in the population, but about the usefulness of that marker in an assay to detect differences that may or may not be relevant to clinical efficacy. Take hemoglobin, for instance, with erythropoietin--I'm playing the other side here, just to see what you think. I mean, even if there is variability in how that relates to clinical outcomes, or how much the spectrum is across the population, one could reasonably devise an equivalency protocol according to a PD marker and look for changes in the hemoglobin to reasonably infer whether, in fact, you had a similar molecule or not, irrespective of that variability.

So I'm just sort of--

DR. PARKINSON: tell you what, Bill, I'll join you as a consultant, and I'll be the erythropoietin specialist. How's that?

[Laughter.]

DR. PARKINSON: Because, you know, one

answer is trying to find clinical settings that are more homogeneous. There the readout--the noise will actually--and you can begin to do that after you study 50,000 patients with erythropoietins. You have a database.

DR. SCHWIETERMAN: Anyway, the point is to talk about the principles that actually--you know, that these invoke. And I think comments on these would be welcome.

DR. DUCHARME: Just a note: I guess ideally what we would recommend for most products is to do a crossover trial, so that every subject is his own control--understanding that we cannot always do that because of the washout.

But that would take care of a lot of the variability that you're talking about between subjects.

DR. PARKINSON: Well, I think that's a very valuable point about design issues, and I will tell you, in the last session the point was brought up that there are limits to what settings you can and cannot use crossover--largely related, as you say,

to either pharmacological or pharmacodynamic half-life.

But--other comments from people? But obviously that's a very clean design--if you could utilize it.

MS. STEIN: I think this will be discussed more tomorrow, but if you have a protein that's immunogenic you can't use that patient for another product.

I think some of the assumptions that I've heard in the discussion of PK and PD are based on having a--quote-- identical molecule. And I guess the question that I would just raise again is: can you ever know, with complex biologics, comparing the drug products, that they're identical? And I would argue that you can't.

DR. DUCHARME: Murray Ducharme.

If the drug is--if one compound is immunogenic, and you have, for example--how do you say that?--antibodies that destroy the protein, basically you will not show same PK/PD. Or, also, if you randomize your study, you may see a sequence

effect.

So I think that is not a limitation, per se to ability of PK/PD study to work. And when we're talking about PK/PD studies right now, we're not saying that you don't need to do a study for immunogenicity later on. I mean, that's topic for tomorrow, as I understand it.

MS. STEIN: I think--you know Dave raised the question in the context of Epo about patient homogeneity, or heterogeneity. The fact is patients are heterogeneous, and not all make antibodies. And so you need a very large population if you're going to analyze crossover populations, to be able to factor in all that variability, and which patients will make antibodies and which ones won't.

And small studies are not going to answer that.

DR. DUCHARME: [Off mike.] It's tomorrow's topic.

MS. STEIN: It's tomorrow's topic--

[Laughter.]

--but, again, it comes to the issue of whether--you know, you're dealing with products that are identical, and in a clinical setting, you

know--products that you assume are identical--and in a clinical setting where you have heterogeneity of patient population, how can you answer these by small studies?

DR. OLESON: Rick Oleson again.

I worked on a compound at Biogen-Avenex, and we had to change our cell line. And one of the things I proposed at a workshop that FDA had on bioequivalence at the time--and this was in a model for PK, but I think it comes up with PD, because PD is concerning to me in terms of variability--is that you see, in a blind setting--it doesn't have to be blind--but basically repeating the reference against--in this case, maybe the innovator's drug versus the new one--in a cohort of subjects--or, in this case when I did this, a cohort of animals--the same two dose levels were repeated in two different sets of animals.

You can do it in a crossover design if you

don't have antibodies coming up. But, in other words, what you're doing is taking, say, a low and a high dose, repeating it in separate sets of animals so you have a comparison with the same agent, done in the same animals, but in two different cohorts and two different dose levels so you get an idea of biological variability--particularly in PD.

Now, in the PK setting in humans, and the PD setting in humans, if you can't do a crossover study for one question--if it's an important enough drug that this might be an avenue to look at--to take your reference agent, repeat it in two different sets of 12, or 15 or however many. I know it's going to increase the cost, but this is a critical endpoint. You don't want to be getting the wrong answer, and you don't want to be getting a false comparison and that will lead you to saying it's not comparable because of the variability.

DR. PARKINSON: So you're suggesting the endpoint would really be range of variability.

DR. OLESON: Right.

DR. PARKINSON: The variance.

DR. OLESON: You have the reference agent. You have variability between two different cohorts

of subjects, treated identically with the same material, so you get an idea, inherently, of all the biological variability within the system--analytically, as well as biological.

DR. PARKINSON: Very interesting.

Other comments that relate to study design and establishment of acceptable limits?

Yes, sir.

DR. FIELDER: Ah--

DR. PARKINSON: Name and serial number.

DR. FIELDER: I can even remember it. I'm Paul Fielder from Genentech.

Touching on the study design, one of the things that, with a lot of protein therapeutics, especially a lot of our monoclonal antibodies, is their non-linear pharmacokinetics. So to do that--to really study the range of what the PK and PD is--I agree, you would need more of a dose-response, or hopefully you establish that

during Phase II, and then you can move into pivotals.

One of the problems, I think, if people try too much with a PD is if you really want to minimize the variability, people are going to tend to overdose. And if you design studies non-clinically and clinically, where you give enough protein, you can essentially drive the pharmodynamic responses to where they're fairly similar, but that's with really overdosing.

So I think if people really try and shoot for some of this and use bioequivalence, we're going to start, you know, really compromising study designs, where people are really trying to design studies that don't show a difference, rather than showing whether there is a difference.

DR. SCHWIETERMAN: Yes, that's a very important point. The assay sensitivity changes depending upon the magnitude of the effect on the PD marker, and I think that that point is well taken.

[Pause.]

DR. DUCHARME: Murray Ducharme, MDS Pharma Services and University of Montreal.

I think the point is very important as it

regards to non-linearity. What we need to remember is that those studies are comparability studies. And so I'm not sure about the dose response--about proving the dose response is the same--but I believe that it would be very important if non-linearity, for example, is related to the dose, then it's very important to study the dose that is the most discriminative of PK/PD.

And then, in addition, what happens very often with biologics, is that you have time-dependent non-linearity. That means that a single-dose study is not enough; that you have to do a steady-state study in addition.

So it's very important to distinguish the two, and make sure that we study what is the most discriminative.

DR. SCHWIETERMAN: Good. Thank you.

DR. VELAGAPUDI: Raja Velagapudi from Barr Laboratories.

I couldn't stand it there, you know, like the conversation that went on. The PK, the linearity--you do these studies to pick up the differences. The whole idea is to pick up the difference. If the PK is the linear range, then PK discriminates well. If the PD already reached a

non-linear curve down or flattened surface, then the gentleman said, you know, that you won't be showing any difference. We may pick up a dose that where the response is flat, and therefore your study is always equivalent.

I would also challenge a little bit more about that. If you take it to the clinical study, where most of the people pick their doses in the near maximal dose, where the response is much flatter than PK, or sometimes in the PD linear range, you basically, after doing the clinical study, you come to the same point: that the products are equal--not because there is a clinical relevance, because you are already on the flat surface of the near maximal dose.

So the utility goes backward, is actually

to figuring out in the linear range where you want to study, where you can pick up the difference in these two [inaudible]--mainly the product.

DR. PARKINSON: Aren't we all in agreement here?

Murray? You're not sure? Okay.

Don't go away, Dr. Velagapudi. Don't go away.

DR. DUCHARME: I'm Murray Ducharme.

I think we're in agreement, but what I was mentioning before is it's a comparability trial, so it's not a trial to show that the dose-response is the same. We have to make sure that we study the dose that is the most discriminative of PK/PD.

DR. VELAGAPUDI: [Off mike.]We agree.

DR. PARKINSON: My goodness. This may be historical.

[Laughter.]

Great.

DR. VELAGAPUDI: The testing is actually to see that the products are different.

DR. PARKINSON: No--you're point was very

well taken. And I actually think--Dr. Fielding, as well--I think that we're all in agreement that if we're really going to do the studies, you should do it at the most sensitive aspect of the dose-response curve. Right.

With an addendum.

DR. FIELDER: I think where we're talking about--I think that's very important during the development, but of course the most important: is there going to be any major differences at a clinically meaningful place?

DR. PARKINSON: Fair enough.

DR. FIELDER: Because I think that will also--but you're absolutely correct. If you want to see the differences, especially with non-linear, the lower you dose the greater you're going to see those differences.

So I think any follow-on should do that, because that will inherently tell you whether the molecules are different or not. But, of course, the true measure is going to be at the clinically relevant dose.

DR. PARKINSON: Fair enough.

Other comments that relate to the use of PK/PD in establishing comparability?

[Pause.]

Yes, there is one--at least one additional comment.

DR. VELAGAPUDI: Raja Velagapudi from Barr again.

Well, one thing we should not forget is: if there are non-linear situations--that means that clinically it's possible only to use in a non-linear range because the therapeutic range is non-linear--in those cases, we have to follow back and then see what the Agency has done for non-linear drugs. We don't want to reinvent another mechanism of approving drugs when there is a similar situation to what we have already fought 10, 15 years to bring the guidelines to non-linear drugs, and then here you come--because it's a protein, we're going to reinvent the world.

So we should follow what we have already with a similar situation and see, you know, how we

can do those things. We should take the guidelines--at least for consideration.

DR. SCHWIETERMAN: Other comments and questions?

[No response.]

Dena, have we answered number three here? What factors affect study design and establishment of acceptable limits? We've touched upon that a fair amount, don't you think?

DR. PARKINSON: Are there any other questions which people feel should be brought up in the context of the conduct of PK/PD with this topic? This is your last chance--well, at least for this meeting.

[Laughter.]

I suspect this may come up--this topic may come up again.

[Laughter.]

Okay. Dr. Hixon, it's yours.

DR. HIXON: Let me do what I did with the last session, and just try to summarize what we've heard, and what areas we seem to have agreement or

disagreement on, and then get feedback if everybody doesn't agree.

It sounds like everyone agrees that there certainly is utility for using PK studies for evaluation of follow-on protein products; and that PK, in itself, may not be enough; that we often have situations where we need to go ahead with further clinical data, but that's a subject for one of tomorrow's sessions.

We had some discussion about the 80-125 limits. And I think, again, we're kind of at the same point as before: that there's really no good rationale for the 80-125, but in terms of looking for acceptable comparability in terms of PK, that may be the best we have until we get some scientific rationale for a different set of limits.

We've also heard some good suggestions in terms of the design of PK and PD studies, and particularly we seem to have good agreement on the fact that PK studies should be designed to use a dose that would be discriminatory and most likely to show differences, instead of a dose at either

end of the dose-response curve that will make products look more similar.

[Pause.]

What am I missing? Any other summaries?

DR. PARKINSON: I think those are the major elements, in terms of action items.

Any other comments from the audience?

Dr. Ducharme?

DR. DUCHARME: Sorry--it's me again.

I just wanted to mention that I think there is a rationale for the plus-or-minus 20 percent. If one considers all the uncertainty when we do a study--the uncertainty in the dose, what is accepted by USP standards, etcetera; the uncertainty in the analytical assays, etcetera--I think plus-or-minus 20 percent is very, very conservative and will ensure you that you will not have a clinical difference.

So I think it's a good--the rationale is good.

DR. FACKLER: Paul Fackler, with Teva. I just want to add my two cents to the 80 to 125

discussion.

I think it was pulled out of thin air many years ago, as the goal post, if you will, for bioequivalence. But I want to reiterate a point that was made this morning: that if the confidence intervals are 80 to 125, the mean differences between the products is often 10 percent or less. Because of the variability of the products, it's the only way to get the confidence intervals to fall within that particular window. And this is log-transform data.

And the other thing I would say is: we have a lot of experience with 80 to 125. I think half the prescriptions in the United States today are filled with generic drugs, all of which were approved with an 80 to 125 confidence interval. So there's some empirical evidence that these limits work for comparability of pharmaceuticals. That's not to say any more than it is; that it was pulled out of thin air.

DR. HIXON: That's a good correction. I really should have said the 80 125 was based on

empirical information, as opposed to not having any other clear scientific reason why the 80-125 was set. But we certainly have relied upon that for years, and so far it has worked.

[Pause.]

Thanks, everybody, for staying this late and participating and providing as much input as you have to the discussion of use of PK/PD.

Have a good evening.

[Whereupon, at 4:37 p.m., the session concluded.]

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